Taking Aim at ALK Across the Blood–Brain Barrier

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The remarkable clinical efficacy of crizotinib has quickly established anaplastic lymphoma kinase (ALK) positivity as a key molecular feature in non–small-cell lung cancer (NSCLC).[1–3] Together with the efficacy of epidermal growth factor receptor (EGFR) inhibitors in EGFR mutant disease, thoracic oncologists have become hungry for new molecular subtypes of NSCLC to identify and control with novel targeted therapies.[4,5] Yet, a series of recent case reports in this journal remind us that significant health gains could be achieved in advanced NSCLC without the need for new targets. Specifically, tremendous progress could be made if we could just inhibit the molecular targets that we already know are important when those targets are located within the central nervous system (CNS).

Both Gandhi et al.[6] and Maillet et al.[7] report cases of ALK+ NSCLC responding to crizotinib outside the CNS, but progressing within the CNS. In a recent retrospective analysis, the lifetime incidence of brain metastases in ALK+ lung cancer appeared similar in patients that either received or never received crizotinib, suggesting that crizotinib was not altering the natural history of the disease in the CNS.[8] Consistent with this, and with these case reports, 13 of 28 ALK+ patients (46%) first progressed on crizotinib within the CNS, with 85% having ongoing extra-CNS disease control at the time.[9] One potential explanation comes from the pharmacokinetic analyses of a single ALK+ patient progressing within the CNS. Five hours after taking 250 mg, the cerebrospinal fluid (CSF) crizotinib concentration was 0.0014 μmol/L with the CSF to plasma ratio only 0.0026.[10] Put another way, the CSF levels in this patient were more than 170-fold lower than the concentration required for 50% growth inhibition in an ALK+ cell line in vitro.[10] If the CNS really is crizotinib's Achilles' heel, then routine surveillance of the CNS should probably be considered for all crizotinib patients, although, in the absence of detailed data, the optimal frequency of this surveillance remains uncertain.

When CNS disease is detected, it may be treatable with radiotherapy. Radiotherapy to sites of progression, in conjunction with continuing the crizotinib was permitted in the early crizotinib trials.[1,9] Although no randomized study has yet addressed the benefit of ongoing crizotinib post-CNS progression, in the face of extra-CNS disease control retrospective data suggest the inhibitor should not be stopped. When patients with either EGFR mutant or ALK+ disease and isolated CNS progression on erlotinib or crizotinib, respectively, received brain radiotherapy and the relevant inhibitor was kept going, further progression took more than 7 months to occur.[9] As radiotherapy may increase the local permeability of the blood–brain barrier, there is also the possibility that the same inhibitor may be more beneficial in the CNS postradiation than it was preirradiation.[11] Consistent with this, Kaneda et al.[12] describe the seemingly exceptional case of an ALK+ patient with progression in a previously irradiated CNS lesion which then responded to crizotinib. Similarly, standard doses of crizotinib produced a response in a mesenchymal epithelial transition factor (MET)-amplified glioblastoma, approximately 5 months after prior radiotherapy.[13]

If CNS progression on crizotinib primarily reflects inadequate drug exposures, then another way of getting ALK+ CNS disease back under control would be to get drugs active against crizotinib-naive cancer into the CNS. An intrathecal formulation of crizotinib has been discussed with Pfizer, but has not yet been prioritized for clinical development. In

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terms of other options, Gandhi et al.[6] reported a prolonged CNS response using a combination of high-dose pemetrexed (900 mg/m^2 q21 days) with high-dose continuous crizotinib (600 mg QD). However, although this case demonstrates that systemically active chemotherapy could be tried in the event of CNS progression, and ALK+ disease does seem more sensitive to pemetrexed than to other cytotoxics, it is unclear which, if any, of the details of their combination regimen can be recommended.[3] For example, pemetrexed at standard doses is also known to have activity in NSCLC CNS metastases.[14] In addition, although we do not know that the previously described CSF levels of crizotinib are representative, if they are, then increasing the crizotinib dose by only two- to threefold is highly unlikely to have achieved active CNS levels.[10] Arguably, the greatest promise for treating ALK+ disease within the CNS comes from the second-generation ALK inhibitors. Both LDK378 and AP26113 have now reported CNS responses within their early phase studies.[15,16] Although this offers some hope to ALK+ patients, it is also important to recognize that no data have yet been presented on either the denominator of CNS disease to assess the reliability of these CNS responses, or their duration.

Discussing the clinical data that is, or is not, available brings us face to face with some of the major issues currently limiting progress in the treatment of NSCLC metastatic to the CNS. If these second-generation inhibitor studies had excluded all patients with CNS disease, then this early hint of CNS efficacy—a potential key differentiator from crizotinib—would have been missed. Yet, unfortunately, many studies of novel agents still routinely exclude patients with asymptomatic and/or untreated parenchymal or leptomeningeal CNS disease. Although the assessment of responses in leptomeningeal disease remains difficult, the Response Assessment in Neuro-Oncology group has now developed guidelines for the assessment of parenchymal metastases within clinical trials.[17] In a disease with such a high lifetime incidence of CNS disease, it also remains surprising that baseline and on therapy CNS imaging is not mandated or standardized within many lung cancer studies. When there is a lack of knowledge about whether a new drug penetrates into the CNS, the best way to determine this is going to be to formally look for CNS activity whenever extra-CNS activity is expected. If there are serious concerns that patients with CNS disease will adversely influence the efficacy signal of a new drug in a trial, then a standalone CNS cohort at the recommended phase II dose could reasonably become a part of routine early drug development. Alternatively, if using local therapies for isolated CNS progression and continuing drug treatment becomes more widely accepted, then it may become standard practice to capture not just overall progression-free survival, but both CNS and extra-CNS progression-free survival values as well, ultimately allowing us to compare these between drugs.[9,17] Modifying our clinical trial designs to reliably capture CNS-related information is a straightforward strategy we could immediately adopt to begin directly addressing CNS metastases in the era of molecular oncology. Aiming at any target across the blood–brain barrier will become much easier once we start to do it with our eyes appropriately open.

REFERENCES

1. Camidge DR, Bang YJ, Kwak EL, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. *Lancet Oncol* 2012;13:1011–1019.
2. Kim D-W, Ahn M-J, Shi Y, et al. Results of a global phase II study with crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC). *ASCO Meeting Abstracts* 2012;30(15_suppl): 7533.
3. Shaw AT, Varghese AM, Solomon BJ, et al. Pemetrexed-based chemotherapy in patients with advanced, ALK-positive non-small cell lung cancer. *Ann Oncol* 2013;24:59–66.
4. Kris MG, Johnson BE, Kwiatkowski DJ, et al: Identification of driver mutations in tumor specimens from 1,000 patients with lung adenocarcinoma: the NCI's Lung Cancer Mutation Consortium (LCMC). 2011 *ASCO Annual Meeting*. Abstract CRA7506.
5. Bunn PA Jr, Hirsch FR, Doebele RC, Camidge DR, Varella-Garcia M, Franklin W. Biomarkers are here to stay for clinical research and standard care. *J Thorac Oncol* 2010;5:1113–1115.
6. Gandhi L, Drappatz J, Ramaiya NH, Otterson GA. High-dose pemetrexed in combination with high-dose crizotinib for the treatment of refractory CNS metastases in ALK-rearranged non-small-cell lung cancer. *J Thorac Oncol* 2013;8:e3–e5.
7. Maillet D, Martel-Lafay I, Arpin D, et al. Ineffectiveness of crizotinib on brain metastases in two cases of lung adenocarcinoma with EML4-ALK rearrangement. *J Thorac Oncol* 2013;8:e30–e31.
8. Shaw AT, Yeap BY, Solomon BJ, et al. Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis. *Lancet Oncol* 2011;12:1004–1012.
9. Weickhardt AJ, Scheier B, Burke JM, et al. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. *J Thorac Oncol* 2012;7:1807–1814.
10. Costa DB, Kobayashi S, Pandya SS, et al. CSF concentration of the anaplastic lymphoma kinase inhibitor crizotinib. *J Clin Oncol* 2011;29:e443–e445.
11. Stemmler HJ, Schmitt M, Willems A, Bernhard H, Harbeck N, Heinemann V. Ratio of trastuzumab levels in serum and cerebrospinal fluid is altered in HER2-positive breast cancer patients with brain metastases and impairment of blood-brain barrier. *Anticancer Drugs* 2007;18:23–28.
12. Kaneda H, Okamoto I, Nakagawa K. Rapid response of brain metastasis to crizotinib in a patient with ALK rearrangement-positive non-small cell lung cancer. *J Thorac Oncol* 2013;8:e32–e33.
13. Chi AS, Batchelor TT, Kwak EL, et al. Rapid radiographic and clinical improvement after treatment of a MET-amplified recurrent glioblastoma with a mesenchymal-epithelial transition inhibitor. *J Clin Oncol* 2012;30:e30–e33.
14. Bearz A, Garassino I, Tiseo M, et al. Activity of pemetrexed on brain metastases from non-small cell lung cancer. *Lung Cancer* 2010;68:264–268.
15. Mehra R, Camidge DR, Sharma S, et al. First-in-human phase I study of the ALK inhibitor LDK378 in advanced solid tumors. *ASCO Proc* 2012; 3007.
16. Gettinger S, Weiss GJ, Salgia R, et al. A first-in-human dose-finding study of the ALK/EGFR inhibitor AP26113 in patients with advanced malignancies. *ESMO 37th Annual Meeting* 2012; Abstract 4390.
17. Lin NU, Lee EQ, Aoyama H, et al. Response assessment in neuro-oncology (A Report of the RANO Group): challenges relating to solid tumor brain metastases in clinical trials, part 1: patient population, response, and progression (Submitted).